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Huxley-type cross-bridge models in largeish-scale musculoskeletal models; an evaluation of computational cost

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ABSTRACT

A Huxley-type cross-bridge model is attractive because it is inspired by our current understanding of the processes underlying muscle contraction, and because it provides a unified description of muscle's mechanical behavior and metabolic energy expenditure. In this study, we determined the computational cost for task optimization of a largeish-scale musculoskeletal model in which muscles are represented by a 2-state Huxley-type cross-bridge model. Parameter values defining the rate functions of the Huxley-type cross-bridge model could be chosen such that the steady-state force-velocity relation resembled that of a Hill-type model. Using these parameter values, maximum-height squat jumping was used as the example task to evaluate the computational cost of task optimization for a skeletal model driven by a Huxley-type cross-bridge model. The optimal solutions for the Huxley- and Hill-type muscle models were similar for all mechanical variables considered. Computational cost of the Huxley-type cross-bridge model was much higher than that of the Hill-type model. Compared to the Hill-type model, the number of state variables per muscle was large (2 vs about 18,000), the integration step size had to be about 100 times smaller, and the computational cost per integration step was about 100 times higher.

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1. Introduction

The importance of forward dynamics musculoskeletal models is broadly recognized in the field of biomechanics (Zajac, 1989; Delp et al., 2007). In these models, muscle-tendon complexes are typically represented by Hill-type models. The phenomenological description of the force-velocity relation as proposed by Hill (1938) is a key element of this muscle model. Albeit simple, the Hill-type muscle model has been successfully used in the study of the mechanics of many tasks, including jumping (Pandy and Zajac, 1991; Bobbert et al., 1996), cycling (van Soest and Casius, 2000) and locomotion (Markowitz and Herr, 2016).

As the relation between mechanical behavior and metabolic energy expenditure (MEE) in whole-body tasks is important, several attempts have been made (e.g. Umberger et al., 2003; Bhargava et al., 2004) to estimate MEE based on a Hill-type description of mechanical behavior of muscle. While the simplicity of the resulting model is attractive from a computational point of view, the approach is conceptually unsatisfying because of the phenomenological nature of the resulting model.

The description of the contractile process proposed by Huxley (1957) is an interesting alternative to the Hill-type model. Conceptually, a Huxley-type cross-bridge model is attractive not only because it is inspired by our qualitative understanding of the underlying processes (cross-bridge cycling), but also because it provides a unified description of mechanical behavior and MEE. On the downside, it is only recently starting to become clear how earlier descriptions of cross-bridge dynamics can be linked to underlying physical processes (e.g. Günther et al., 2018). Furthermore, Huxley-type cross-bridge models are computationally unattractive, if only because they are mathematically described by partial differential equations instead of ordinary differential equations. This was recognized many years ago by Zahalak (1981), who proposed an approximation of the Huxley-type cross-bridge model in which the distribution of the attached cross-bridges over their bond length was assumed to have a prescribed form (e.g. normal distribution). Unfortunately, this distribution-moment approximation was never applied in largeish-scale musculoskeletal models.

Recently, Lemaire et al. (2016) developed a 2-state Huxley-type muscle-tendon complex model in state space form, and showed that the mechanical behavior of rat soleus muscle during in-vitro stretch-shortening cycles can be described equally well by a Hill-type model and the newly developed Huxley-type cross-bridge

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model. Importantly, in that study a method was described to ensure that the force exerted by this Huxley-type cross-bridge model of the contractile process is equal to the force in the series elastic element connected to it.

Before investigating how well MEE can be predicted by such a Huxley-type cross-bridge model, the computational cost of task optimization for a whole-body task using this recently developed Huxley-type cross-bridge model should be evaluated. In addition, it should be investigated if, when parameter values of this Huxley-type cross-bridge model are chosen appropriately, the mechanical behavior for the optimal solution is similar to that obtained using a Hill-type model.

2. Methods

2.1. Outline of this study

The example task considered in this study is maximum-height squat jumping, a relatively simple whole-body movement task that has been widely studied using forward dynamics (e.g. Pandy and Zajac, 1991; van Soest and Bobbert, 1993). Neural input to muscles is optimized with respect to jump height for two models, using a genetic algorithm. These two forward dynamics models are identical in most respects; differences exist only in the representation of contractile element (CE) dynamics. In most respects, the models are identical to that described in van Soest and Bobbert (1993). A between-models comparison is made of the optimal solutions and of computational cost.

2.2. Model description - skeletal system

The skeletal system is modelled as a 2D sagittal-plane linkage of 4 rigid body segments, connected in hinge joints. The two feet are combined into a single "feet" segment, and the same is done for lower and upper legs; the fourth segment represents head-arms-trunk (HAT). Segment parameters are as reported in van Soest and Bobbert (1993). Equations of motion in Newton-Euler form were derived automatically using the algorithm described in Casius et al. (2004). Foot-ground contact at the distal end of the foot during push-off was also modelled as a hinge joint.

2.3. Model description - muscle models

The skeletal model is driven by 6 muscle-tendon complex (MTC) models representing the Soleus, Gastrocnemius, Vasti, Rectus Femoris, Gluteals and Hamstrings. The Hill-type model and the Huxley-type cross-bridge model share the same description of activation dynamics, CE force-length relation and series elastic element (SEE) force-length relation. As explained in detail in Lemaire et al. (2016), the model of the activation process is inspired on Curtin et al. (1998). Normalized muscle stimulation is linked to intracellular Ca^{2+} concentration (used as state variable) through first-order dynamics with activation faster than deactivation. The fraction of cross bridges participating in the contractile process (normalized active state) is linked to intracellular Ca^{2+} concentration via a saturating, sigmoid relation. For the range of CE lengths in which active force production is possible, the CE force-length relation was modelled as described in Lemaire et al. (2016). For SEE length larger than SEE slack length, the SEE force-length relation was modelled as a second-order polynomial as in van Soest and Bobbert (1993).

For the Hill-type model, relative parameter values for the force-velocity relation were set identical for all muscles; the dependence of maximum shortening velocity on CE length and on active state as described in the appendix of van Soest and Bobbert (1993)

was not implemented here. For the Huxley-type cross-bridge model, the steady-state force-velocity relation follows from the rate functions that define how (un)binding of cross-bridges depends on bond length (i.e. the distance between adjacent actin and myosin binding sites). In this study, the rate functions as described in Lemaire et al. (2016) were used; see Appendix A for details. Values for parameters f_1 , g_2 and g_3 in these rate functions were optimized numerically with the aim to minimize the difference between the resulting steady state force-velocity relation (at optimum length and maximum activation) and the corresponding Hill-type force-velocity relation.

Muscle-tendon dynamics followed from the fact that, neglecting muscle mass (and neglecting parallel elastic element forces), SEE force and CE force should be equal. For the Hill-type model, this allows (at any time) calculation of the CE velocity from MTC length (which is a function of joint angle), CE length (which is a state variable) and active state (which is the output of the activation dynamics). This calculation is based on Hill's force-velocity relation as described above; see van Soest and Bobbert (1993) for details. For the Huxley-type cross-bridge model, the situation is different; here, the CE state is constituted by the distribution of n (fraction of attached cross-bridges) over discretized bond length x . In Lemaire et al. (2016), bond length was discretized in about 18,000 bins for each muscle. In the present study, we evaluated if the number of bins could be reduced by one or more orders of magnitude without compromising the simulation outcomes. It was found that reduction of the number of bins by one order of magnitude already resulted in inconsistent results; for the task studied here, the number of bins could not be reduced by a factor of more than 5. As it is not guaranteed that this smaller number of bins would also yield valid results in simulations of other tasks, it was decided to report results for the slightly conservative value of about 18,000 bins per muscle. In terms of number of state variables, this implies that the contractile dynamics is described by about 18,000 time-dependent state variables per muscle, as opposed to the single state variable (CE length) used in the Hill-type model. CE force follows from this distribution, while SEE force follows from the difference between MTC length and CE length. As these CE and SEE forces should be equal at all times, it follows that their time derivatives should also be equal; the equality constraint, stating that CE and SEE force derivatives should be equal, is solved for CE velocity at each point in time. In this study, the number of bins was reduced until reduction by another order of magnitude resulted in an unacceptable difference between CE force and SE force. Thus, the number of bins was chosen slightly conservatively. For more details, see Lemaire et al. (2016). Parallel elastic elements (PEE), although present in both muscle models, play no role in the optimal solutions to be discussed.

2.4. Model description - interaction between muscles and skeleton

Muscles and skeleton have a two-way interaction, that (for each muscle) is defined by a polynomial function that has joint angle(s) as input and MTC length as output; moment arm as a function of joint angle follows directly from this function (see van Soest and Bobbert, 1993). On the one hand, MTC length and velocity (inputs of the muscle models) are calculated from the kinematics of the skeletal model. On the other hand, the effect of each muscle on the acceleration of the skeleton is represented by its contribution to net joint moment(s) around the joint(s) spanned by that muscle, calculated from muscle force and moment arm(s).

2.5. Model description - initial state, inputs and outputs

The initial state of the skeletal system corresponds to static equilibrium in a squatted position and is identical to that used in

van Soest and Bobbert (1993). The muscle load sharing problem in this position is solved by having bi-articular MTC's (Gastrocnemius, Rectus Femoris, Hamstrings) generate a small force, arbitrarily set to 100 N, and requiring the lumped mono-articular MTC's (referred to as Soleus, Vasti, Gluteals) to generate a force that is consistent with static equilibrium. For the Hill-type model, muscle stimulation, intracellular Ca^{2+} concentration and CE length can be calculated from this requirement. For the Huxley-type cross-bridge model, muscle stimulation, intracellular Ca^{2+} concentration, CE length and the complete discretized distribution $n(x)$ can be calculated from this requirement. Inputs of the musculoskeletal model are STIM(t) for each MTC. In this study, bang-bang control is used; consequently, STIM(t) for each MTC is parametrized by the point in time at which STIM switches from the initial value to the maximal value of 1.0. In a strict sense, the outputs of both musculoskeletal models are the values of all state variables as a function of time; the values of all other variables of interest can be calculated from the time history of the inputs and the state variables.

2.6. Forward dynamics simulation, task, optimization criterion, and optimization algorithm

For any set of STIM switching times (the inputs of both musculoskeletal models), a forward dynamics simulation can be carried out; in this study, an improved Euler integration scheme is used to obtain a numerical solution. Based on extensive testing, the fixed integration step size was set at 10^{-5} s; it was confirmed that simulations with a tenfold and hundredfold smaller step size resulted in essentially the same solution. The task considered in this study is maximum-height squat jumping. Thus, formulation of the optimization problem was straightforward: for each muscle, find the time at which STIM should be switched to its maximal value in order to maximize the peak height reached by the center of mass (COM) of the skeletal system. In order to obtain the peak COM height corresponding to any set of STIM switch times, a simulation of the push-off phase was done; peak COM height was calculated from the state at take-off. The optimization problem was solved using the genetic algorithm described in van Soest and Casius (2003). In this study, 16-bit binary encoding of input parameters and a population size of 100 were used. Each optimization was started from a random initial population. For both the Hill-type and the Huxley-type cross-bridge model, 5 independent optimizations were carried out in order to ascertain that the solution found was near-globally optimal.

3. Results and discussion

3.1. Rate functions in Huxley-type cross-bridge model can be tuned to yield a desired steady-state force-velocity relation

In this study, it was intended to maximize the resemblance between the Hill-type and the Huxley-type cross-bridge model in all respects but the description of the contraction process. To that aim, the rate parameters governing cross-bridge (de)coupling in the Huxley-type cross-bridge model were tuned in order to make the steady-state force-velocity relation similar to the force-velocity relation of the Hill-type model. As can be seen from Fig. 1, this was successful; the rate parameters of the Huxley-type cross-bridge model can be chosen such that the steady-state normalized force-velocity relation (at optimum length and at maximum activation) of the Huxley-type cross-bridge model is very similar to its Hill-type counterpart for concentric contractions, and reasonably similar for eccentric contractions.

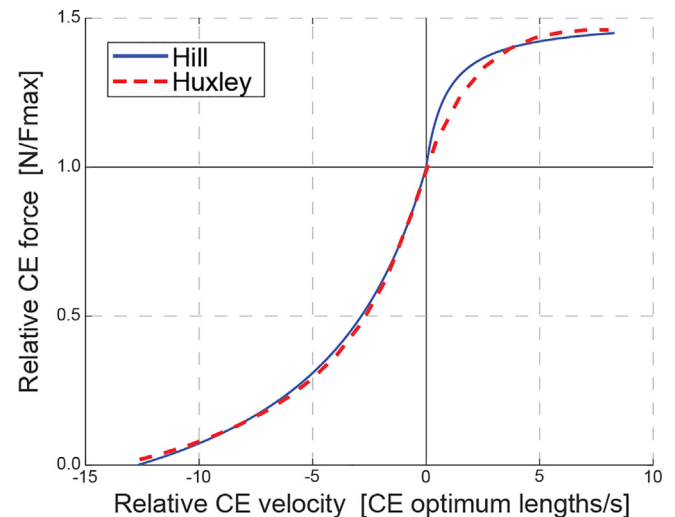


Fig. 1. Normalized force-velocity relation for the Hill-type model at optimum CE length and maximal activation (blue solid line) and corresponding steady-state force-velocity relation of the Huxley-type model (red dashed line), using $f_1 = 943$, $g_2 = 3023$, $g_3 = 1382$ (see Lemaire et al. (2016) for details). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. Optimizations converge successfully for both the Hill-type and the Huxley-type cross-bridge model

For both models, the genetic algorithm was run 5 times, from independent random initial guesses. For each model, optimal jump height differed less than 0.001 m between optimizations. Furthermore, we note that, due to the random components in the genetic algorithm, highly unusual states are visited during the optimization process. The successful convergence of the Huxley-type model thus indicates that the optimization of this model is sufficiently robust. To our knowledge, this is the first time that a 2-state Huxley-type cross-bridge model is successfully used in task optimization of a largeish-scale musculoskeletal model.

3.3. Optimal solutions for the Hill-type model and the Huxley-type model are similar

Given the similarity of the two models, which are identical in all respects but the description of the contraction process, one would expect the optimal solutions to be similar. Indeed, maximal jump height (relative to the ground) was 1.516 m for the Hill-type model and 1.508 for the Huxley-type model, which corresponds to a jump height relative to upright standing of 0.435 m for the Hill-type model and 0.427 for the Huxley-type model. The difference in maximal jump height was thus in the order of 0.01 m, which is quite small. Furthermore, as is shown in Fig. 2, optimal stimulation patterns (described by the time at which each muscle starts to be maximally stimulated, relative to take-off) are similar for both models; it can also be seen from Fig. 2 that push-off duration was 0.294 s for the Hill-type model and 0.295 s for the Huxley-type model.

Optimal solutions for the Hill-type and Huxley-type models were similar for all mechanical variables considered, including horizontal and vertical ground reaction forces (Fig. 3), skeletal kinematics (Fig. 4, in which segment angles are plotted against segment angular velocities), CE force (shown as a function of CE velocity for Vasti in Fig. 5), and CE mechanical work (shown for all muscles in Fig. 6). In order to further investigate the similarity of the overall dynamics of both models, we applied the optimal stimulation pattern for the Hill-type model to the Huxley-type

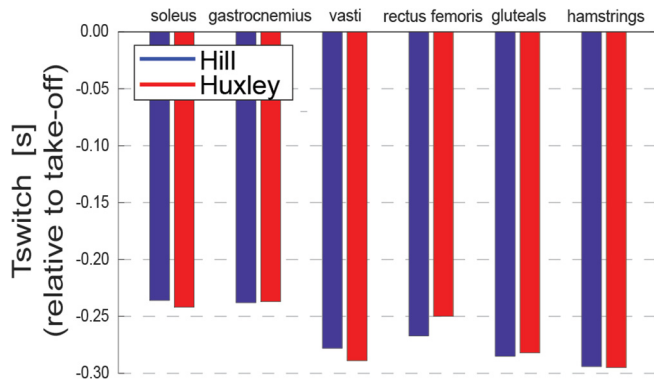


Fig. 2. Time (relative to take-off) at which muscle stimulation is switched to its maximal value for all muscles in the optimal solution for the Hill-type (blue bars, leftmost bar of each pair) and Huxley-type (red bars, rightmost bar of each pair) models. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

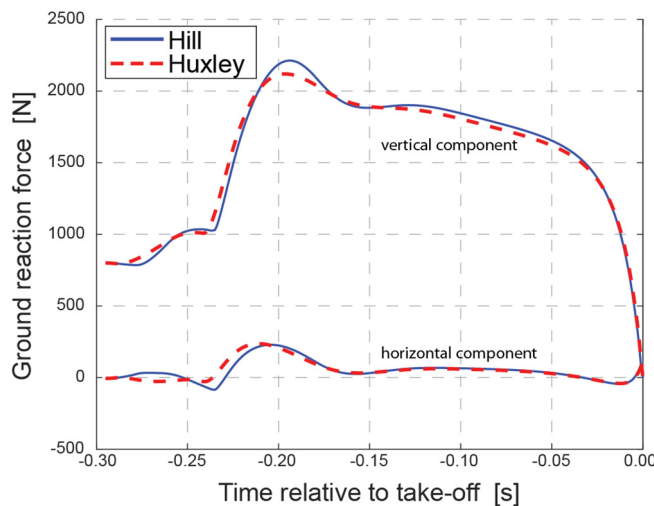


Fig. 3. Horizontal and vertical ground reaction force as a function of time (relative to take-off) for the optimal solutions for the Hill-type model (blue solid lines) and Huxley-type model (red dashed lines). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

model, and vice versa. In both cases, this resulted in a well-coordinated movement, with jump heights about 0.005 m smaller than that for the optimal solutions.

Finally, in Fig. 7 the time evolution of the cross-bridge distribution over bond length is shown, which is the one aspect of the Huxley-type cross-bridge model that has no counterpart in the Hill-type model.

3.4. Computational cost of the Huxley-type cross-bridge model is much higher than that of the Hill-type model

Both models were implemented in C, and run under Linux (kernel version 4.14) on a Single Core(TM) i7-4770 CPU running at 3.40 GHz for profiling. Profiling was done using PERF, a standard Linux profiling tool. Computational cost of both models was evaluated by considering simulations of the optimal solutions for both models, using improved Euler integration with an integration step size of 10^{-5} s. For the Hill-type model, a single simulation entailed 1.5 billion instructions, which corresponded to a CPU time of about 0.18 s. Thus, this simulation runs approximately in real time on the hardware used. In contrast, a single simulation of the optimal solution for the Huxley-type model entailed 70 billion instructions,

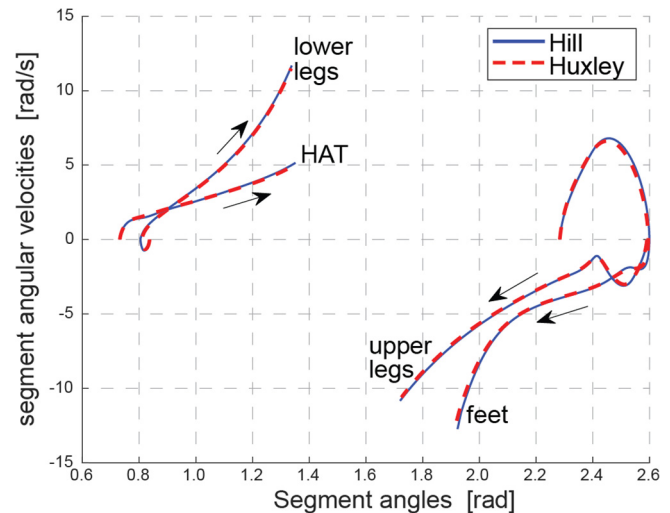


Fig. 4. Segment angular velocity as a function of the corresponding segment angle for feet, lower legs, upper legs and Head-Arms-Trunk (HAT). Blue solid lines represent the push-off phase of the optimal solution for Hill-type model, red dashed lines represent the push-off phase of the optimal solution for the Huxley-type model. Segment angles are defined relative to a right horizontal line through the distal end of the segment (counterclockwise positive). Arrows indicate the direction of time progression. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

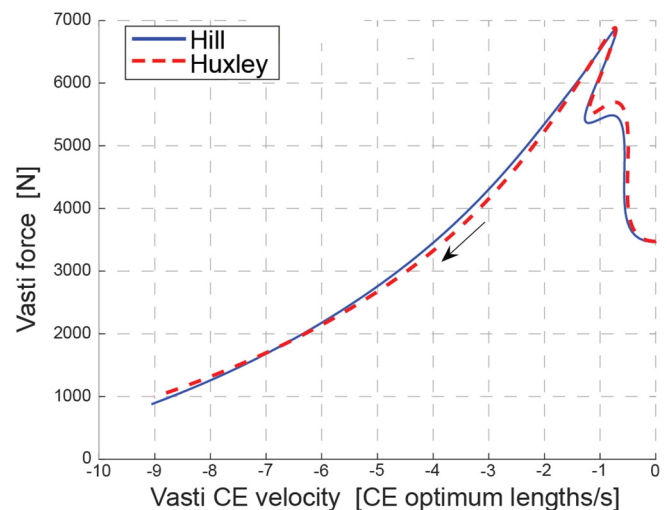


Fig. 5. Vasti contractile element (CE) force as a function of Vasti CE velocity for the push-off phase of the optimal solution of the Hill-type (blue solid line) and Huxley-type (red dashed line) models. Arrow indicates the direction of time progression. Force values are for two legs combined. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

which corresponded to a CPU time of about 21 s. In relative terms, the computation time for a simulation of the Huxley-type model is about 100 times higher than that for the Hill-type model when using the same fixed-step integrator.

Simulations of musculoskeletal models are usually performed using more sophisticated integration algorithms than the improved Euler algorithm used here, such as the Adams-Bashforth-Moulton predictor-corrector algorithm with variable step size and variable order (Shampine and Gordon, 1975). Unfortunately, use of the latter integration algorithm did not result in a reduction in the computational cost for the Huxley-type model. In contrast, use of this integration algorithm for the Hill-type model resulted in a drastic reduction in the number of integration steps, reducing the number of instructions for simulation of the optimal

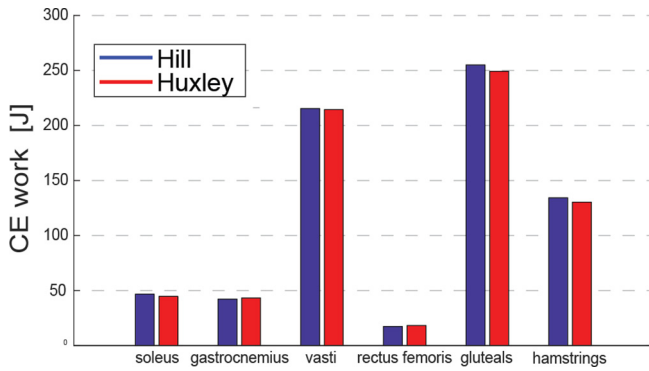


Fig. 6. Mechanical work done by the contractile elements (CE) of all muscles during the push-off phase in the optimal solution for the Hill-type model (blue bars, leftmost bar of each pair) and Huxley-type model (red bars, rightmost bar of each pair). Work values are for two legs combined. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

push-off phase to about 16 million, corresponding to a CPU time of about 2 ms. In comparison with these values for the Hill-type model, the CPU time required for the Huxley-type model is about 10,000 times larger.

Given the number of simulations carried out in a typical optimization, which for the task studied here is in the order of 10^5 , it is clear that it is barely feasible to run the optimizations carried out in this study on a single core. Fortunately, the genetic algorithm for optimization used in this study (see van Soest and Casius (2003) for details) is very suitable for parallel processing; in this study about 100 cores were used in parallel for the optimizations.

4. General discussion and conclusion

In this study, we investigated the computational cost of using a 2-state Huxley-type cross-bridge model in optimization of a largeish-scale musculoskeletal model. We have shown that the parameter values defining the rate functions of the Huxley-type cross-bridge model can be chosen such that the steady-state

force-velocity relation is similar to that of a Hill-type model. We have further shown, to our knowledge for the first time, that it is feasible to perform task optimization for a largeish-scale musculoskeletal model containing this Huxley-type cross-bridge description of muscle dynamics. We have confirmed that, as expected, the optimal solution for the Huxley-type model is similar to that of an equivalent Hill-type model for all mechanical variables considered. In terms of computational cost, the Huxley-type model was found to require an integration step size that is about 100 times smaller than that of the Hill-type model, with a cost per step that is about 100 times higher; in total, at this point the computational cost of the Huxley-type model is about 10,000 times higher than that of the Hill-type model.

It might be interesting to reconsider Zahalak's idea (Zahalak, 1981) to make an assumption on the shape of the distribution of the attached cross-bridges over bond length, and calculate macroscopic variables such as muscle force from that distribution. The advantage of such a “distribution-moment” approach is that the number of state variables describing the distribution is reduced drastically relative to the approach used in this study (see Lemaire et al. (2016) for details): 3 states per muscle for the distribution-moment model, compared to about 18,000 states per muscle for the Huxley-type cross-bridge model used in this study. However, it is clear from Fig. 7 that, for the Huxley-type cross-bridge model used in this study, the distribution of the attached cross-bridges over bond length is quite different from the normal distribution assumed in the distribution-moment model. This does not directly disqualify the distribution-moment approach, however, because muscle force (the macroscopic variable of key interest in this study) depends on the integral of $x \cdot n(x)$ with respect to bond length x . Be that as it may, when using the distribution-moment approach by itself, there is no way to ascertain that the distribution assumption is sufficiently good to obtain results for the macroscopic variables of interest that are similar to those of the underlying Huxley-type cross-bridge model; to ascertain this, results of a full-blown Huxley-type cross-bridge model are required for comparison.

In comparison to the computational cost of optimizations of the Hill-type model, that of the Huxley-type model used in this study is very high. Most importantly, the integration step size required

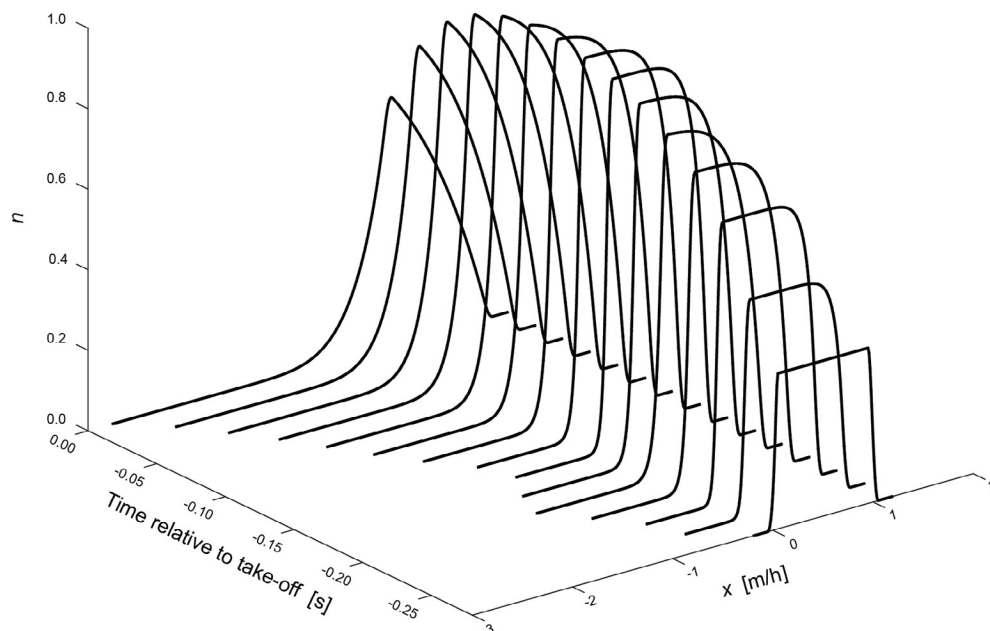


Fig. 7. Time evolution (relative to the instant of take-off) of the distribution $n(x)$ for Vasti, where bond length x is normalized with respect to maximum bond length h at which cross-bridges can attach, and where n is the fraction of coupled cross-bridges, for the optimal solution of the Huxley-type model.

for sufficiently accurate simulation of the macro-scale Hill-type contraction dynamics can be much larger than that required for simulation of the micro-scale cross-bridge dynamics in the Huxley-type cross-bridge model, even though the macro-scale behavior of the two models is very similar. In an absolute sense, the computational cost could be acceptable when large-scale parallel processing can be used during optimization. Further profiling and software optimization are expected to reduce the computational cost. Furthermore, the method used to convert the partial differential equation describing the Huxley-type cross-bridge model to a system of ordinary differential equations, as well as the computational method to solve these equations may be improved. This may lead to a further decrease of the computational cost, making optimizations of 3D models containing more segments and (most importantly) more muscles feasible in the near future.

In sum, in this study we have evaluated the computational cost of task optimization of a largeish-scale Huxley-type musculoskeletal model. Furthermore, we have shown that the mechanical behavior of such a largeish-scale Huxley-type musculoskeletal model is very similar to that of an equivalent Hill-type model when adequate values are chosen for the Huxley rate parameters. Given these outcomes, we intend to investigate next if the Huxley-type cross-bridge model can be used to predict metabolic energy consumption at the level of contractions of a single muscle and at the level of whole-body motions.

Conflict of interest

The authors declared that there is no conflict of interest.

Appendix A

The Huxley MTC model used in the present study is a modified version of the classic two-state model (Huxley, 1957), in which the time course of the distribution of the fraction of attached cross-bridges (n), over their bond length (x) is modelled:

$$\frac{\partial n}{\partial t} - u \frac{\partial n}{\partial x} = f(x) - (f(x) + g(x))n \quad (\text{A1})$$

with $f(x)$ and $g(x)$ the attachment and detachment rate functions, respectively. The input variable u is the relative velocity of the actin and myosin filaments. The rate functions in the present study are as follows. $f(x)$ is modelled as a piecewise constant function;

$$f(x) = \begin{cases} f_1, & \text{if } 0 \leq x \leq h \\ 0, & \text{otherwise} \end{cases} \quad (\text{A2})$$

with f_1 the attachment rate parameter. $g(x)$ is modelled as two quadratic functions with both their extreme values and shape parameters determined by a single parameter:

$$g(x) = \begin{cases} g_2 x^2 + g_3, & \text{if } x \leq 0 \\ g_3 (x - h)^2 + g_3, & \text{if } x \geq h \\ 0, & \text{otherwise} \end{cases} \quad (\text{A3})$$

with g_2 and g_3 the detachment rate parameters. Note that $g(x) = 0$ in the region where cross-bridges can attach (i.e. Huxley's $g_1 = 0$). This formulation is uncommon in that it would result in zero energy expenditure during steady state isometric contraction. However, in the present study only mechanical behavior is considered and the Hill force velocity curve could be adequately modelled with the current formulation of the rate functions.

The stepwise nature of Eqs. (A2) and (A3) would require a small integration step size during simulations. Therefore, to improve

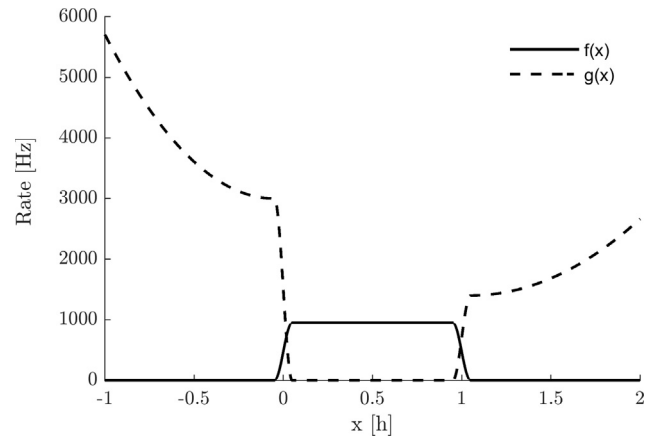


Fig. A1. Rate functions of the Huxley muscle model. Rate of attachment ($f(x)$, solid line) and detachment ($g(x)$, dashed line) of cross-bridges as a function of normalized bond length x according to Eq.'s (A2) and (A3). For all simulations in this study f_1 , g_2 and g_3 equalled 943, 3023 and 1382, respectively.

numerical tractability, the rate functions were smoothed using a sine function in an interval of 0.1 h around the transition points, resulting in rate functions with a continuous first derivative, as depicted in Fig. A1. It was found that the smoothing did not materially change model behavior, but did reduce computational cost.

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